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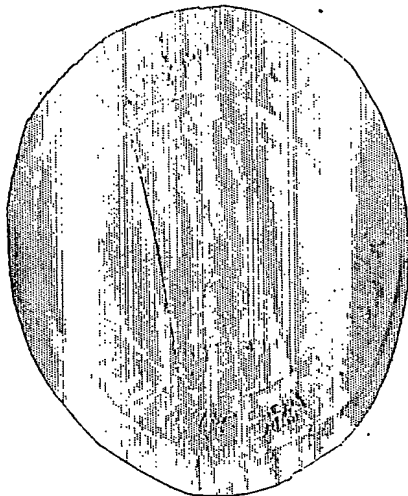
PCT THE PATENTS ACT, 1970

It is hereby certified that annexed hereto is a true copy of Application & Provisional Specification of the extract of Patent Application No.555/CHE/2003, dated 04/07/2003 by M/s. Orchid Chemicals & Pharmaceuticals Limited, having its registered office at Orchid Towers, 152, Village Road, Nungambakkam, Chennai 600 034, Tamil Nadu, India.

.....In witness thereof

I have hereunto set my hand

Dated this the 14th day of July 2004



M. S. Venkataraman

(M.S. VENKATARAMAN)

Assistant Controller of Patents & Designs

[Signature]

PATENT OFFICE BRANCH
GOVERNMENT OF INDIA
Guna Complex, 6th Floor, Annex.II
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PRIORITY DOCUMENT
SUBMITTED OR TRANSMITTED IN
COMPLIANCE WITH
RULE 17.1(a) OR (b)

FORM 1
THE PATENTS ACT, 1970
APPLICATION FOR GRANT OF A PATENT (Section 5(2), 7, 54, 135 and Rule 39)

We, Orchid Chemicals & Pharmaceuticals Ltd., an Indian company having its registered office at orchid Towers, 152, Village Road, Nungambakkam, Chennai-600 034, Tamilnadu, India hereby declare

1.(a) that we are in possession of an invention titled AN IMPROVED PROCESS FOR THE PREPARATION OF A CEPHALOSPORIN COMPOUND

(b) that the provisional specification relating to this invention is filed with this application.

(c) that there is no lawful ground of objection to the grant of a patent to us.

2. further declare that the inventors for the said invention are

1. Pandurang Balwant Deshpande

C-1 "CEEEROS"

Plot No. 32 (New) 1st Avenue,

Indira nagar

Chennai - 600 020, Tamilnadu, India

2. Parven Kumar Luthra

H-85, S-1, TNHB Flats

Valmiki Nagar, Thiruvannmiyur

Chennai 600 041, Tamilnadu, INDIA

3. Pratik Ramesh Sathe

30/A, VJ Flats 9/9, Valmiki Street,

Thiruvannmiyur, Chennai -600041

Tamilnadu, INDIA

3. that we are the assignee of the true and first inventors

4. that all belonging to India and citizens of India

5. that our address for service in India is as follows;

Dr. C. B. Rao

Orchid Chemicals & Pharmaceuticals Ltd.,

Orchid Towers,

152, Village Road,

Nungambakkam,

Chennai-600 034, India.

6. We, the true and first inventors for this invention declare that the applicant herein is our assignee

(Signed) Pandurang Balwant Deshpande
Pandurang Balwant Deshpande

(Signed) Parven Kumar Luthra
Parven Kumar Luthra

(Signed) Pratik Ramesh Sathe
Pratik Ramesh Sathe

8. that to the best of our knowledge, information and belief, the fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of patent to us on this application

9. following are the attachments with the application

a. provisional specification (8 pages, in triplicate)

b. abstract of the invention (1 page, in triplicate)

c. fee Rs. 3000.00 (three thousand rupees only) in cheque bearing 420368 dated June 30, 2003, drawn on ICICI bank, Chennai.

SSS
C-1
4/1/2003

FORM 2
THE PATENTS ACT, 1970

PROVISIONAL SPECIFICATION

(SECTION 10)

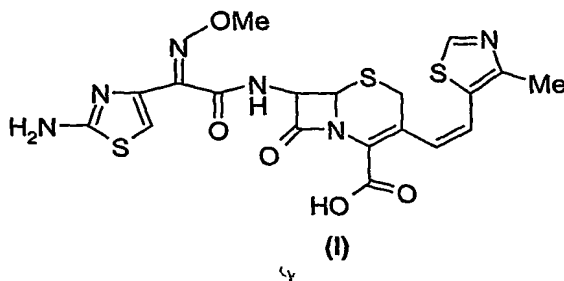
**AN IMPROVED PROCESS FOR THE PREPARATION OF
A CEPHALOSPORIN COMPOUND**

**Orchid Chemicals & Pharmaceuticals Ltd.
an Indian Company having its registered office at
Orchid Towers,
152, Village Road,
Nungambakkam,
Chennai-600 034, India.**

The following specification describes the nature of the invention and the manner in which it has to be performed:

Field of the Invention

The present invention relates to a process for the preparation of 7- α -aminoacyl-cephalosporin derivatives having the general formula (I). More particularly, the present invention relates to a process for the preparation of Cefditoren of the formula (I).



Background of the Invention

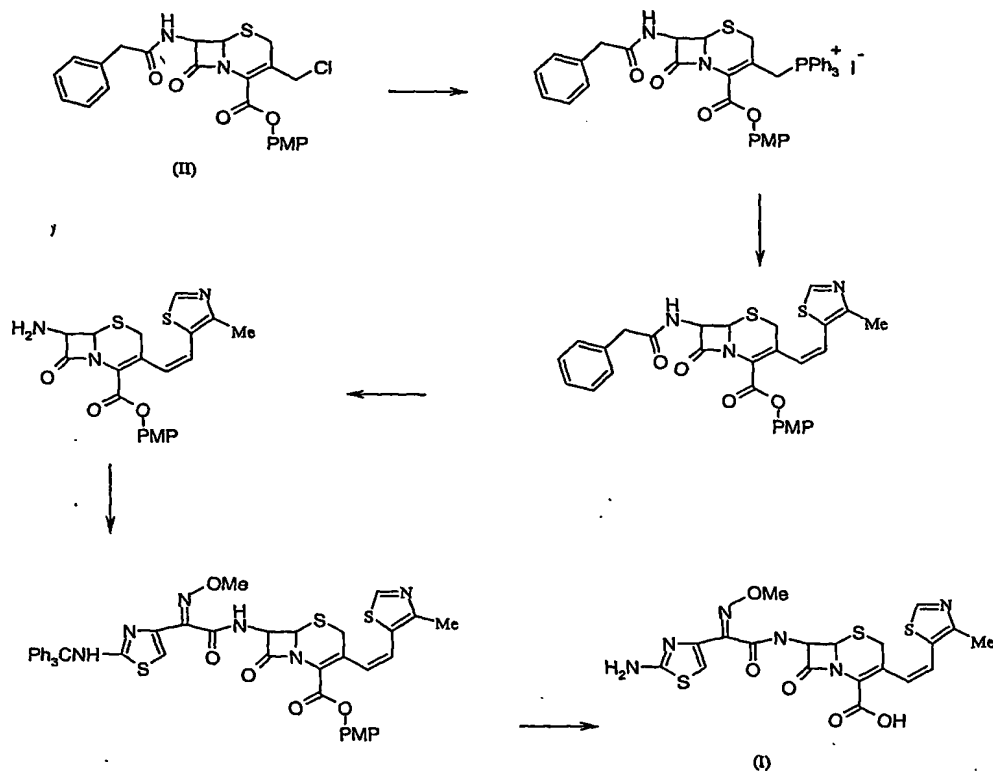
Cefditoren has low toxicity to mammals but exhibits a very broad antibacterial spectrum against positive-bacteria and gram-negative bacteria. Cefditoren is known to be a highly excellent therapeutic agent, which has been extensively utilized for the therapeutic treatments and preventive treatments of bacterial infections caused, by a variety of gram-positive bacteria and gram-negative bacteria.

Originally Cefditoren was disclosed in US patent number 4,839,350. This patent also discloses various processes for the preparation of Cefditoren.

US patent Nos. 5,616,703 and 6,235,897 discloses a process for the depletion of 7-amino-3-[(E)-2-(4-methyl-5-thiazolyl)vinyl]-3-cephem-4-carboxylic acid in Z/E mixtures of 7-amino-3-[2-(4-methyl-5-thiazolyl)vinyl]-3-cephem-4-carboxylic acid a) by subjecting an amine salt of a Z/E mixture of 7-amino-3-[2-(4-methyl-5-thiazolyl)vinyl]-3-cephem-4-carboxylic acid to crystallization and converting this amine salt into 7-

amino-3-[2-(4-methyl-5-thiazolyl)vinyl]-3-cephem-4-carboxylic acid, or b) by subjecting the Z/E mixture to chromatography.

Chem. Pharm.Bull. 39, (1991), 2433 discloses a process which involves conversion of GCLE (II) into Wittig salt, Wittig reaction with 5-formyl-4-methylthiazole, separation of isomer by fractional crystallization followed by column chromatography, deprotection to get free amine, reaction with protected MAEM followed by deprotection to get free acid (I). The E/Z isomer separation involves column chromatography hence yield is less.



wherein PMP denotes p-methoxy phenyl

The foregoing processes are associated with many problems such as poor yield and quality, difficult to commercialization, impurity and percentage of E isomer content is high. Hence there is a need to develop a process, which is easy to commercialize, and which yields good quality as

well as quantity. We focused our research to find a process and finally achieved identifying a clean process for producing the title compound of the invention, which contains less percentage of E isomer.

Objective of the Invention

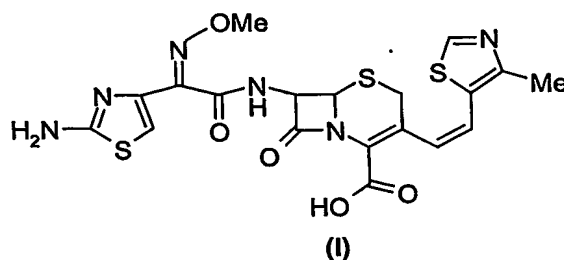
The main objective of the present invention is to provide a process for the preparation of 7- α -aminoacyl-cephalosporin derivatives of the general formula (I), which contains less percentage of E isomer.

Another objective of the present invention is to provide a stable process for the preparation of 7- α -aminoacyl-cephalosporin derivatives of the general formula (I), which is easy to commercialize.

Another objective of the present invention is to provide a high yielding process with good quality.

Summary of the Invention

Accordingly, the present invention provides a process for the preparation (6R,7R)-7-[2-amino-4-thiazolyl[(methoxyimino)acetyl]amino]-3-[2-(4-methyl-5-thiazolyl)vinyl]-3-cephem-4-carboxylic acid derivatives of the formula (I)

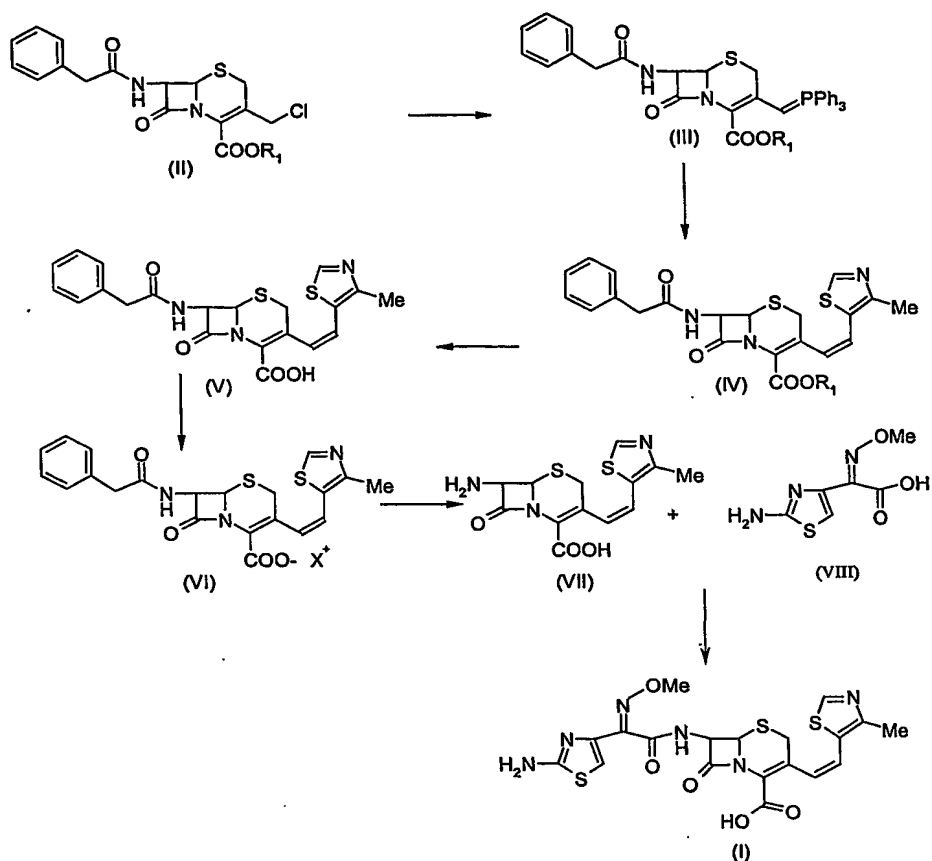


The said comprising the steps of :

- i) converting the compound of formula (II) wherein R_1 represents carboxy protecting group to a compound of the formula (III) using Wittig reagent in the presence of solvent and alkali iodide,

- ii) reacting the compound of formula (III) with 4-methyl-5-formyl-thiazole in presence of absence of lithium chloride in the presence of solvent at a temperature in the range of $-20\text{ }^{\circ}\text{C}$ to $50\text{ }^{\circ}\text{C}$ to produce a compound of formula (IV) wherein R_1 is as defined above,
- iii) deesterifying the carboxy protecting group of compound of the formula (IV) using an acid in the presence of solvent at a temperature in the range of $0\text{ }^{\circ}\text{C}$ to $50\text{ }^{\circ}\text{C}$ to yield compound of formula (V),
- iv) converting the compound of formula (V) to compound of formula (VI) wherein X represents a counter ion which forms a salt in the presence of a base and solvent,
- v) neutralizing the compound of formula (VI) followed by enzymatic hydrolysis to produce compound of formula (VII),
- vi) reacting compound of formula (VII) or its reactive derivative with compound of formula (VIII) or its reactive derivative in the presence of solvent and to produce compound of formula (I), and
- vii) isolating the compound of formula (I).

The process is shown in Scheme-2



Scheme-2

Detailed description of the invention

In an embodiment of the present invention, the group represented by R^1 is selected from (C_1-C_6) alkyl group such as methyl, ethyl, propyl, isopropyl, t-butyl and the like; p-methoxybenzyl, p-nitrobenzyl, o-chlorobenzyl, diphenylmethyl and the like.

In yet another embodiment of the present invention the solvent used in step (i) may be selected from methylene chloride, ethylene dichloride, acetone, ethyl methyl ketone, methyl isobutyl ketone, toluene, IPE, hexane, ethyl acetate, water and the like or mixtures thereof.

In an embodiment of the present invention the reaction with 4-methyl-5-formyl-thiazole (or 4-methylthiazol-5-carbaldehyde) is carried out using solvents such as DMF, DMAc, isopropyl alcohol, methylene chloride, acetonitrile and the like or mixture thereof.

In yet another embodiment of the present invention the deesterification is carried out using phenol/trifluoroacetic acid, anisole/trifluoroacetic acid, formic acid, PTSA, hydrochloric acid using solvent such as halogenated hydrocarbon, esters, alkanols, water and the like or mixture thereof.

In yet another embodiment of the present invention the conversion in step (iv) is carried out in the presence of solvent selected from water, acetone, DMF, THF, DMAc, DMSO, halogenated alkanes and the like using base such as sodium hydroxide, lithium hydroxide, potassium hydroxide, ammonia, alkali/alkali metal bicarbonates, alkali/alkali metal carbonates, or organic base such as tertiary butyl amine, benzyl amine, dibenzyl amine, diethyl amine, diisopropyl amine, dicyclohexyl amine, benzathine, octyl amine, and the like.

In yet another embodiment of the present invention the neutralization in step (v) is carried out using inorganic acid like H_2SO_4 , HCl, phosphoric acid and the like.

In yet another embodiment of the present invention the solvent used in step (vi) is selected from halogenated hydrocarbons, esters, ethers, cyclohexane, and the like.

In another embodiment of the present invention the reactive derivative of compound of formula (VII) includes silylated derivative, or salts with bases such as TMG, TEA, DCHA, benzathine, octyl amine, sodium or potassium salt, and the like.

In still another embodiment of the present invention compound of formula (VII) may contain some amount of (E)-isomer.

In yet another embodiment of the present invention the reactive derivative of compound of formula (VIII) includes acid halide, acid anhydride, active amide, ester, etc. and the like.

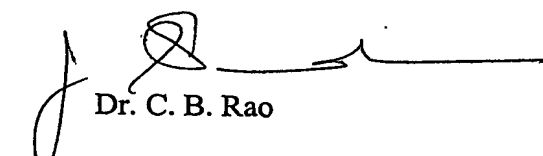
In another embodiment of the present invention the reaction of compound of formula (VII) with compound of formula (VIII) can be carried out by the method disclosed in our own Indian patent application number 389/MAS/2002

In yet another embodiment of the present invention the reaction of compound of formula (VII) with compound of formula (VIII) can be carried out if required in the presence of base.

The foregoing technique has been found to be markedly attractive, both from commercial point of view, as well as from manufacturing viewpoint, and affords good quality of Cefditoren of the formula (I).

Many other beneficial results can be obtained by applying disclosed invention in a different manner or by modifying the invention with the scope of disclosure.

Dated this third (3rd) day of July 2003
for Orchid Chemicals & Pharmaceuticals Ltd.,


Dr. C. B. Rao
Dy. Managing Director